

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
13 December 2001 (13.12.2001)

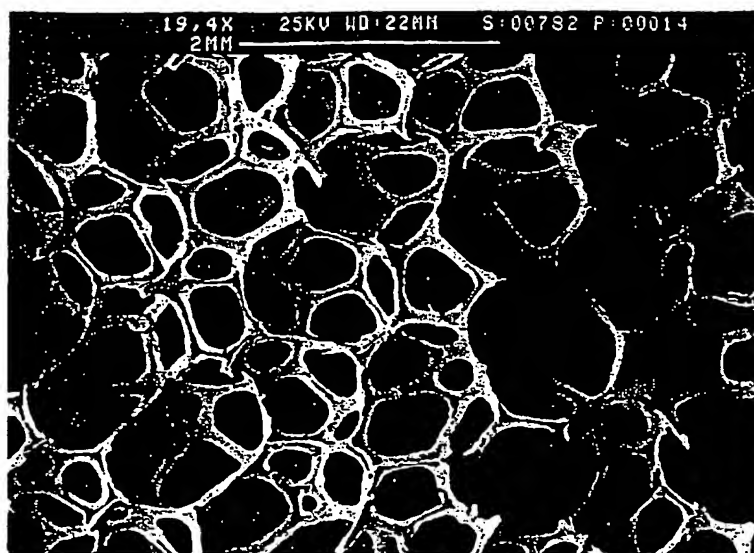
PCT

(10) International Publication Number  
WO 01/94274 A1

- (51) International Patent Classification<sup>7</sup>: C04B 38/06, 35/447, A61K 6/033, A61L 27/12
- (74) Agent: BOULT WADE TENNANT; Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).
- (21) International Application Number: PCT/GB01/02507
- (22) International Filing Date: 7 June 2001 (07.06.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 0013870.1 7 June 2000 (07.06.2000) GB
- (71) Applicant (for all designated States except US): UNIVERSITY COLLEGE LONDON [GB/GB]; Brook House, 2-16 Torrington Place, London WC1E 7HN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): KNOWLES, Jonathan [GB/GB]; 254 Sandycombe Road, Kew, Surrey TW9 3NP (GB). CALLCUT, Suzanne [GB/GB]; 15 Cromwell Road, Cheshunt, Herts EN7 6AS (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report

[Continued on next page]

(54) Title: FOAMED CERAMICS



(57) Abstract: A method for the production of a glass-reinforced ceramic foam material for use in biomedical applications and comprising hydroxyapatite and a biocompatible glass, which method comprises: a) providing a foam carrier; b) providing a slip comprising a liquid carrier and either (i) a biocompatible glass particulate and a ceramic particulate selected from one or both of hydroxyapatite and apatite or (ii) a composite ceramic-glass particulate comprising a biocompatible glass with one or both of apatite and hydroxyapatite; c) coating the foam carrier with the slip; and d) heating the slip-coated foam carrier at a temperature sufficient to substantially burn out the precursor foam carrier.

WO 01/94274 A1

WO 01/94274 A1



*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

### Foamed Ceramics

The present invention relates to a method for producing a ceramic foam material and, in particular, a glass-reinforced ceramic foam material for use in biomedical applications and comprising hydroxyapatite and a biocompatible glass.

The apatite group of minerals are based on calcium phosphate, with stoichiometric hydroxyapatite having a molar ratio of Ca/P of 1.67. Hydroxyapatite has the chemical formula  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ .

There is increasing interest in the development of biomaterials which more closely match the chemical composition, mechanical properties and structure of bone mineral, resulting in faster bone bonding between implant and host. Porous bio-ceramic materials may provide secure fixation of an implant as a result of bony ingrowth and mechanical interlock.

Hydroxyapatite has potential for hard tissue replacement and/or augmentation and there are a number of porous hydroxyapatite based implant materials currently available on the commercial market. Many of these materials are derived from either animal cancellous bone or coral, which is hydrothermally treated so as to convert the natural ceramic component into hydroxyapatite, while preserving the natural porous structure. For example, Endobon (RTM) is produced via the hydrothermal conversion of bovine cancellous bone. A second method utilises the natural structure of coral which by a hydrothermal processing method converts the calcium carbonate based coral to hydroxyapatite, while retaining the porous structure of the coral.

These materials have inherent limitations. For example, naturally-derived materials may contain heavy metals which have been incorporated into the structure. Furthermore, there is limited information and control on the physical characteristics in many of these porous structures, and in some cases there is limited control over the chemical composition. The materials are therefore susceptible to variability in their structure and hence the tissue reaction on implantation is variable. Porous hydroxyapatite produced using synthetic hydroxyapatite, while offering a more controllable material in terms of both chemistry and morphology, has low bioactivity. Substitutions may be made into the structure, but these make the material unstable at high temperatures and thus difficult to process without loss of beneficial ions (such as  $\text{CO}_3^{2-}$ ) or decomposition.

Ceramic foams are conventionally formed by infiltrating a polymer foam with a slip, which is a fine slurry of ceramic particles in a fluid, such as water. When the aggregate is fired, the slip bonds to the polymer foam to give an image of the original foam, which is burnt off. Ceramic foams may also be made by chemical vapour deposition on to a substrate of reticulated carbon foam.

The present invention aims to provide a method for the manufacture of porous materials with improved properties which are suitable for use in medical applications.

Accordingly, the present invention provides a method for the production of a glass-reinforced ceramic foam material for use in biomedical applications and comprising hydroxyapatite and a biocompatible glass, which method comprises:

- (a) providing a foam carrier;
- (b) providing a slip comprising a liquid carrier and either (i) a biocompatible glass particulate and a ceramic particulate selected from one or both of hydroxyapatite and apatite or (ii) a composite ceramic-glass particulate comprising a biocompatible glass with one or both of apatite and hydroxyapatite;
- (c) coating the foam carrier with the slip; and
- (d) heating the slip-coated foam carrier at a temperature sufficient to substantially burn out the foam carrier.

Foams are three-dimensional cellular solids and may be classified as either open-celled or closed-cell. The relative density of a cellular material is defined as the ratio of the density of the cellular material to that of the solid material. For bone, the relative density generally falls within the range of from 0.05 to 0.7, i.e. 30 to 95 % porous. Furthermore, determination of the relative density of a porous structure can give an indication of the degree of pore connectivity within the structure. For cancellous bone, a structure with a relative density of less than approximately 0.2 (i.e. 80 % porous) is generally classed as open, while one with a relative density of more than approximately 0.2 (i.e. 80% porous) will possess a closed (non-interconnected) porosity. For this invention, open interconnected porosity is of primary interest.

By the term biocompatible glass as used herein is meant that the glass is substantially free of any metal ions which are not tolerated by the body (except

for  $\text{Al}^{3+}$ , provided that the amount is small).

The slip advantageously further comprises a deflocculant to enable the particles in the slip to remain in suspension for extended periods of time. Suitable deflocculants include anionic deflocculants, for example one or more of sodium carbonate, sodium oxalate, sodium phosphate, sodium hydroxide, sodium silicate, sodium hexametaphosphate and sodium polyacrylate. The use of a deflocculant allows the suspension in the liquid carrier to accurately and uniformly coat the foam carrier. A particularly preferred deflocculant is commercially available under the name Dispex N40.

The choice of a suitable deflocculant may be made on the basis of the surface charge of the slip. Surface charge may be determined by conventional means, for example by zeta potential measurements. The rheology of the slip may also be assessed to optimise the deflocculant concentration and also the solids concentration in suspension.

The slip may further comprise one or both of a surfactant and a dispersant.

The slip preferably has a pH in the range of from 7 to 11, preferably from 8 to 10, more preferably from 8.5 to 9.5.

The slip preferably has a viscosity  $\leq 30$  Cps, more preferably  $\leq 25$  Cps, still more preferably from 5 to 20 Cps. Viscosity may be measured using a cone and plate viscometer. The slip should have a viscosity to enable it to substantially coat the foam carrier uniformly. The viscosity and rheological properties of the slip may be adjusted by altering the relative

amounts of the liquid carrier and the ceramic and glass particulates. The viscosity may also be adjusted by the addition of a deflocculant.

5           The solids concentration in the slip is preferably adjusted to ensure that the ceramic/glass foam has a substantially open structure. A slip concentration that is too high may make complete removal of excess slip difficult from the foam with  
10           the result of blocked pores. Conversely, too low a slip concentration may result in incomplete coating of the foam carrier.

          The foam carrier preferably comprises a  
15           reticulated foam which will typically have a pore density of from 30 to 80 pores per inch, preferably 40 to 70 pores per inch, more preferably 45 to 60 pores per inch. The foam carrier is formed from a material that can be burnt off to leave a substantially  
20           unsupported ceramic/glass foam. The foam carrier is preferably formed from a resilient and flexible material such as a polymer or a rubber, although paper and cardboard materials may also be used for some applications. The preferred foam carrier is based on  
25           polyurethane and may be obtained from Commercial Foam Ltd. Such a material, which is resilient and flexible, may be compressed following the application of the slip. In this manner, excess slip is removed and once the compression force is removed the foam  
30           reverts to its original form. Compression may be achieved by passing the foam between rollers for example. Hydrophilic polymers may also be preferably used for the foam carrier.

35           In a preferred aspect of the present invention, a reticulated foam carrier of polyurethane is immersed in a bath of the slip. The foam carrier is removed

from the bath and then compressed to remove the excess slip. Once dry, the ceramic/glass impregnated carrier foam is heated to burn off the polyurethane, thus leaving a substantially unsupported reticulated ceramic/glass foam.

Preferably, substantially all of the glass particulate has a particle size of less than 100  $\mu\text{m}$ , more preferably less than 85  $\mu\text{m}$ . Similarly, preferably substantially all of the ceramic particulate or the ceramic-glass particulate has a particle size of less than 100  $\mu\text{m}$ , more preferably less than 85  $\mu\text{m}$ .

The ceramic particulate may be selected from one or both of hydroxyapatite and apatite, including substituted-hydroxyapatite and substituted-apatite. The ceramic particulate may preferably be either a spray dried and/or calcined powder, or it may be directly obtained from the as-precipitated filter cake. A preferred hydroxyapatite is commercially available from Plasma Biotel Ltd.

The biocompatible glass for the glass particulate may be produced by conventional glass melting techniques. The glass is preferably melted in a platinum crucible at a temperature of from 1000 to 1300°C and preferably then quenched to prevent devitrification. The glass is typically then ground for up to 24 hours in a porcelain ball mill to produce a fine powder. A suitable ball is available from Pascal Ltd.

The biocompatible glass is preferably based on an oxide composition comprising one or more of  $\text{CaO}$ ,  $\text{P}_2\text{O}_5$ ,  $\text{MgO}$ ,  $\text{Na}_2\text{O}$  and  $\text{Al}_2\text{O}_3$  and will typically be contained in the slip in an amount of up to 10 wt.% based on the



total weight of the particulate, preferably up to 5 wt.%, more preferably from 1 to 3 wt.%.

Suitable biocompatible glasses for use in the present invention are, for example, one or more of: a two oxide glass, such as  $\text{CaO-P}_2\text{O}_5$ ; a three oxide glass, such as  $\text{CaO-Na}_2\text{O-P}_2\text{O}_5$ ,  $\text{CaO-MgO-P}_2\text{O}_5$  or  $\text{CaO-CaF}_2\text{-P}_2\text{O}_5$  glass; and a four oxide, such as  $\text{CaO-Na}_2\text{O-Al}_2\text{O}_3\text{-P}_2\text{O}_5$  and a  $\text{CaO-MgO-CaF}_2\text{-P}_2\text{O}_5$ . Other components may be incorporated into the biocompatible glass based upon  $\text{CaO}$  and  $\text{P}_2\text{O}_5$ , provided that the metals of the oxide used in the formation thereof are compatible with the body.

A particularly preferred biocompatible glass for use in the present invention is a two oxide  $\text{CaO-P}_2\text{O}_5$  glass. The mole ratio of  $\text{CaO}$  to  $\text{P}_2\text{O}_5$  in these glasses may vary within wide limits but preferably is from 20:80 to 80:20 mol %. The glass having a mole ratio of  $\text{CaO:P}_2\text{O}_5$  of about 50:50 is particularly preferred. If  $\text{CaF}_2$ , or any other compound containing calcium, is used as the source of  $\text{F}^-$  ions (see below), the amount of  $\text{Ca}$  in this compound is added to the amount of  $\text{CaO}$  when determining the above ratio. Thus by using such a compound the amount of  $\text{CaO}$  in the glass may be reduced if appropriate.

Suitable examples of the liquid carrier include water, preferably double distilled water, alcohols, such as methanol and propan-2-ol, and hydrocarbons, such as trichloroethane.

The slip may suitably be prepared by combining the constituents into a homogenous mixture. For example, the glass constituent may first be ground dry for up to 24 hours. Particulate hydroxyapatite may then be added to the particulate glass in an amount to

give a glass addition of, for example, up to 5 wt.%.  
A suspending medium is also added in the form of a  
solvent. For glasses that are soluble in aqueous  
media, the solvent is preferably substantially water  
5 free and methanol may advantageously be used as the  
solvent if the glass is degradable. The solvent and  
glass/ceramic mixture is then mixed and optionally  
ground for up to 24 hours. The slip is then dried for  
example by gentle heating at a temperature of up to  
10 80°C for up to 24 hours. When dry, the friable powder  
may be passed through sieves to give a fine free  
flowing powder of preferably less than 85  $\mu\text{m}$  that may  
be pressed. The liquid carrier, for example water,  
may then be added to the mixed powder to form a slip  
15 or slurry, together optionally with the deflocculant.

The ceramic particulate/glass particulate will  
generally be present in the liquid carrier in an  
amount of from 50 to 80 wt.%, more preferably 55 to 75  
20 wt.%, still more preferably 60 to 70 wt.%, still more  
preferably approximately 65 wt.%.

For certain applications, for example dental  
applications, the slip may further comprise a source  
25 of fluoride ions. The source of fluoride ions  
preferably comprises an alkali metal or alkaline earth  
metal fluoride and suitable examples include one or  
more of  $\text{CaF}_2$ ,  $\text{NaF}$  and  $\text{MgF}_2$ . The source of fluoride  
ions may be incorporated in the biocompatible glass  
30 or, alternatively, may be provided as a separate  
component in the slip.

The slip-covered foam carrier is preferably dried  
prior to the burn-out step. Allowing the liquid  
35 carrier to evaporate from the ceramic slip coating is  
advantageous because excess liquid during the burn-out  
step can affect the properties of the final

ceramic/glass foam and may result in cracking during subsequent heat-treatment. The slip-covered foam carrier may advantageously be heated to facilitate evaporation of the liquid carrier.

5

It will be appreciated that the burn-out temperature will depend upon the nature of the foam carrier. Burn-out should preferably be carried out slowly in order to avoid creation of pressures due to decomposition of the foam carrier and evaporation of any residual moisture. Sufficient amounts of oxygen or air should preferably be supplied so that substantially complete burn-out of the foam carrier can occur. Burn-out is therefore advantageously carried out in a ventilated furnace. Heating of the ceramic slip is carried out at a rate and temperature sufficient to substantially burn-out the precursor foam carrier.

Following burn-out of the foam carrier, the resulting substantially unsupported ceramic/glass foam may be sintered under conditions to achieve the desired phases and microstructure. Alternatively, the unsupported ceramic/glass foam may be coated itself with slip to form a second coating thereon. The slip may have the same composition as the initial slip or may have a different composition. The slip-coated ceramic/glass foam is then preferably allowed to dry. This process may be repeated one or more times to build up a layered structure prior to sintering. Further slip coatings may be applied to a "green" unsupported ceramic/glass foam or to a sintered ceramic/glass foam.

The choice of sintering temperature and sintering atmosphere will depend upon the nature of the ceramic/glass particulate and also the desired

properties of the material, for example microstructure and chemistry. It will be appreciated that the sintering temperature and atmosphere must be chosen carefully to avoid decomposition of the ceramic material.

The final phase composition of the sintered material will depend upon the starting materials and the sintering temperature. The glass-reinforced ceramic foam will typically comprise one or more of the following phases: hydroxyapatite,  $\beta$ -TCP and  $\alpha$ -TCP (tricalcium phosphate).

In a preferred embodiment of the present invention, following substantial evaporation of the liquid carrier, the substantially dry ceramic/glass coated foam carrier may undergo a stepped heat-treatment for foam burn-out and densification by sintering. The optimum parameters for the burn-out step will depend on the foam being used. However, coated foams, such as polyurethane, are typically heated at a rate of from 1 to 5°Cmin<sup>-1</sup>, preferably 1 to 3°Cmin<sup>-1</sup>, and held at a burn-out temperature of from 550 to 650°C, preferably approximately 600°C for up to approximately 1 to 2 hours. During the burn-out stage air may be passed through the furnace to ensure substantial removal of the foam. Once burn-out of the foam is complete, the unsupported ceramic/glass foam may be heated directly from the burn-out temperature, at a rate typically up to approximately 5°Cmin<sup>-1</sup>, to a sintering temperature appropriate for the ceramic/glass powders, typically from 1100 to 1400°C, more typically 1200 to 1350°C, still more typically approximately 1250°C. Alternatively, the unsupported ceramic/glass may be cooled to room temperature and then sintered.

On cooling, the sintered bodies are removed from the furnace and may be machined into the desired geometry. The resulting glass-reinforced ceramic foam material may be provided in the form of, for example, blocks, cylinders and granules.

The sintered ceramic-glass foam produced according to the method of present invention typically has a compression strength of from 0.01 to 0.09 MPA, preferably from 0.02 to 0.09 MPA, more preferably from 0.04 to 0.09 MPA.

The foamed ceramic-glass material produced by the method according to the present invention may be used as a synthetic bone material, including dental materials, for example for use in bone reconstruction and augmentation, implants, and compaction graft-type fillers and for making hydroxyapatite-polymer composites.

The present invention also provides a glass-reinforced ceramic foam material for use in biomedical applications and comprising hydroxyapatite and a biocompatible glass and optionally a source of fluoride ions.

The present invention also provides a glass-reinforced ceramic foam material whenever produced by a method as herein described.

The present invention also provides a synthetic bone material which comprises a glass-reinforced ceramic foam material as herein described.

The present invention also provides a composition which comprises a glass-reinforced ceramic foam material or a synthetic bone material as herein

described, together with a pharmaceutically acceptable diluent or carrier.

5 The present invention also provides a bone implant, filler, cement, tissue engineering scaffold, synthetic bone graft or drug-delivery device which comprises a glass-reinforced ceramic foam material, a synthetic bone material or a composition as herein described.

10

The present invention also provides a glass-reinforced ceramic foam material, a synthetic bone material or a composition as herein described for use in a method of treatment of the human or animal body by surgery or therapy.

15

The present invention will now be described further with reference to the following Figures, provided by way of example, in which:

20

Figure 1 shows a comparison of the compression strength between two sintered glass-reinforced ceramic foam materials according to the present invention. The material comprises hydroxyapatite and approximately 2 wt.% of a  $\text{CaO-MgO-P}_2\text{O}_5$  glass, based on the total weight of the hydroxyapatite and the glass. The precursor foam carrier had a pore density of 45 pores per inch. The first material was formed by applying a single coating of slip onto the precursor foam carrier, while the second material was formed by applying a second coating of slip.

30

Figure 2 shows the same comparison as Figure 1 but for a foam carrier having a pore density of 60 pores per inch.

35

Figure 3 shows a comparison of the compression strength between two sintered glass-reinforced ceramic foam materials according to the present invention. The material comprises hydroxyapatite and approximately 2 wt.% of a  $\text{CaO-MgO-CaF}_2\text{-P}_2\text{O}_5$  glass, based on the total weight of the hydroxyapatite and the glass. The precursor foam carrier had a pore density of 45 pores per inch. The first material was formed by applying a single coating of slip onto the precursor foam carrier, while the second material was formed by applying a second coating of slip.

Figure 4 shows the apparent density for a range of a sintered glass-reinforced ceramic foam materials according to the present invention comprising hydroxyapatite and approximately 2 wt.% (based on the total weight of the hydroxyapatite and the glass) of one of the following glasses:  $\text{CaO-MgO-P}_2\text{O}_5$ ,  $\text{CaO-MgO-CaF}_2\text{-P}_2\text{O}_5$ ,  $\text{CaO-CaF}_2\text{-P}_2\text{O}_5$  or  $\text{CaO-Na}_2\text{O-P}_2\text{O}_5$ . The materials were formed by applying a single coating of slip onto the precursor foam carrier. Precursor foam carriers with pore densities of 45 and 60 pores per inch were used.

Figure 5 shows the apparent density for the same materials featured in Figure 4. In this case, however, a second coating of slip was applied to the precursor foam carriers.

Figure 6 is a SEM micrograph of a sintered glass-reinforced ceramic foam material according to the present invention (magnification x 19.4, one coating applied). The material comprises hydroxyapatite and approximately 2 wt.% of a  $\text{CaO-MgO-P}_2\text{O}_5$  glass, based on the total weight of the

hydroxyapatite and the glass. The precursor foam carrier had a pore density of 45 pores per inch.

Figure 7 is a SEM micrograph of a sintered glass-reinforced ceramic foam material according to the present invention (magnification x 19.8, one coating applied). The material comprises hydroxyapatite and approximately 2 wt.% of a CaO-Na<sub>2</sub>O-P<sub>2</sub>O<sub>5</sub> glass, based on the total weight of the hydroxyapatite and the glass. The precursor foam carrier had a pore density of 60 pores per inch.

Figures 8 (a) and (b) shows a comparison of the compression strength between a variety of sintered glass-reinforced ceramic foam materials according to the present invention. A comparison with pure hydroxyapatite is provided. A comparison is also provided for single and double coatings. The materials comprise hydroxyapatite and approximately 2 wt.% of the glass materials recited below in Table 1 based on the total weight of the hydroxyapatite and the glass. The precursor foam carrier had a pore density of 45 pores per inch.

Table 1

	Na <sub>2</sub> O (mol%)	CaO (mol%)	P <sub>2</sub> O <sub>5</sub> (mol%)	CaF (mol%)	MgO (mol%)
CNP 0100	35%	20%	45%	0%	0%
CNP 0191	31%	24%	45%	0%	0%
CNP 0193	27%	28%	45%	0%	0%
CNP 0197	23%	32%	45%	0%	0%
CNP 0409	19%	36%	45%	0%	0%
CNP 0054	15%	40%	45%	0%	0%
CPF 0138	0%	21.25%	63.75%	15%	0%
CPMg 0117	0%	21.25%	63.75%	0%	15%
CPMgF 0112	0%	21.25%	63.75%	7.5%	7.5%



With reference to Figures 1 to 3 and 8 (a) and (b), it is clear that the application of two coatings of the slip results in a higher ultimate compression strength compared with just one coating of the slip.

5 With reference to Figures 4 and 5, it can be seen that the apparent density generally increases with an increase in the pore density. With reference to Figures 6 and 7, sintered glass-reinforced ceramic foam materials according to the present invention can

10 be seen to have a three-dimensional cellular form with open interconnected porosity.

The glass-reinforced ceramic foam material according to the present invention has enhanced

15 mechanical and biological properties and a highly controlled reticulated foam structure.

The material may be used for space filling and in tissue regeneration. It may also be used to act as a

20 carrier for both inorganic and organic species, due to the extremely high surface area and the interconnected porosity. For example, the glass-reinforced ceramic foam material may be used to carry agents such as bone morphogenetic proteins (BMPs) to enhance fracture

25 healing and agents to control infection and suppress destructive aspects of the host response.

Because the ceramic-foam material is glass-reinforced it can sustain higher loads (compared with

30 non-glass-reinforced materials) and will therefore be integrated more quickly into surrounding tissue. This has particular implications for patients, as it will mean shortened recovery times and enhanced regeneration of lost hard tissue.

**CLAIMS:**

1. A method for the production of a glass-reinforced ceramic foam material for use in biomedical applications and comprising hydroxyapatite and a biocompatible glass, which method comprises:
  - (a) providing a foam carrier;
  - 10 (b) providing a slip comprising a liquid carrier and either (i) a biocompatible glass particulate and a ceramic particulate selected from one or both of hydroxyapatite and apatite or (ii) a composite ceramic-glass particulate comprising a biocompatible glass with one or both of apatite and hydroxyapatite;
  - 15 (c) coating the foam carrier with the slip; and
  - 20 (d) heating the slip-coated foam carrier at a temperature sufficient to substantially burn out the precursor foam carrier.
2. A method as claimed in claim 1, wherein the slip further comprises a deflocculant.
- 25 3. A method as claimed in claim 2, wherein the deflocculant is an anionic deflocculant preferably selected from one or more of sodium carbonate, sodium oxalate, sodium phosphate, sodium hydroxide, sodium silicate, sodium hexametaphosphate and sodium polyacrylate.
- 30 4. A method as claimed in any one of the preceding claims, wherein the slip has a pH in the range of from 7 to 11, preferably from 8 to 10, more preferably from 8.5 to 9.5.

5. A method as claimed in any one of the preceding claims, wherein the foam carrier is a reticulated foam having a pore density of from 30 to 80 pores per inch, preferably 40 to 70 pores per inch, more preferably 45 to 60 pores per inch.

6. A method as claimed in any one of the preceding claims, wherein the foam carrier is formed from a material selected from a polymer and/or a rubber.

7. A method as claimed in claim 6, wherein the foam carrier comprises polyurethane and/or a hydrophilic polymer.

8. A method as claimed in any one of the preceding claims, wherein the slip has a viscosity of less than 30 Cps.

9. A method as claimed in any one of the preceding claims, wherein substantially all of the glass particulate has a particle size of less than 100  $\mu\text{m}$ , preferably less than 85  $\mu\text{m}$ .

10. A method as claimed in any one of the preceding claims, wherein substantially all of the ceramic particulate or the ceramic-glass particulate has a particle size of less than 100  $\mu\text{m}$ , preferably less than 85  $\mu\text{m}$ .

11. A method as claimed in any one of the preceding claims, wherein the liquid carrier comprises water and/or a hydrocarbon.

12. A method as claimed in claim 11, wherein the liquid carrier comprises methanol.

13. A method as claimed in any one of the preceding

claims, wherein the biocompatible glass is based on an oxide composition comprising one or more of CaO, P<sub>2</sub>O<sub>5</sub>, MgO, Na<sub>2</sub>O and Al<sub>2</sub>O<sub>3</sub>.

- 5 14. A method as claimed in any one of the preceding claims, wherein the biocompatible glass is contained in the slip in an amount of up to 10 wt.% based on the total weight of the particulate, preferably up to 5 wt.%, more preferably from 1 to 3 wt.%.
- 10 15. A method as claimed in any one of the preceding claims, wherein the slip further comprises a source of fluoride ions.
- 15 16. A method as claimed in claim 15, wherein the source of fluoride ions comprises an alkali metal or alkaline earth metal fluoride.
- 20 17. A method as claimed in claim 16, wherein the source of fluoride ions is selected from one or more of CaF<sub>2</sub>, NaF and MgF<sub>2</sub>.
- 25 18. A method as claimed in claim in any one of claims 15 to 17, wherein the source of fluoride ions is incorporated in the biocompatible glass.
- 30 19. A method as claimed in any one of the preceding claims, wherein the biocompatible glass is selected from a CaO-P<sub>2</sub>O<sub>5</sub> glass, a CaO-Na<sub>2</sub>O-P<sub>2</sub>O<sub>5</sub> glass, a CaO-MgO-P<sub>2</sub>O<sub>5</sub> glass, a CaO-Na<sub>2</sub>O-Al<sub>2</sub>O<sub>3</sub>-P<sub>2</sub>O<sub>5</sub> glass, a CaO-CaF<sub>2</sub>-P<sub>2</sub>O<sub>5</sub> glass and a CaO-MgO-CaF<sub>2</sub>-P<sub>2</sub>O<sub>5</sub> glass.
- 35 20. A method as claimed in any one of the preceding claims, wherein the slip further comprises one or both of a surfactant and a dispersant.
21. A method as claimed in any one of the preceding

claims, wherein the slip-covered foam carrier is dried prior to the burn-out step.

22. A method as claimed in 21, wherein the slip is  
5 heated at a temperature of up to 100°C to facilitate evaporation of the liquid carrier prior to burn-out of the foam carrier.

23. A method as claimed in any one of the preceding  
10 claims, wherein burn-out of the foam carrier is carried out at a temperature in the range of from 550 to 650°C.

24. A method as claimed in any one of the preceding  
15 claims, further comprising the step of forming a second coating of slip on the ceramic-glass foam following burn-out of the foam carrier.

25. A method as claimed in any one of the preceding  
20 claims, further comprising the step of sintering the ceramic-glass foam following burn-out of the foam carrier.

26. A method as claimed in claim 25, wherein  
25 sintering is carried out at a temperature in the range of from 1200 to 1350°C.

27. A method as claimed in claim 25 or claim 26,  
wherein the sintered ceramic-glass foam has a  
30 compression strength of from 0.01 to 0.09 MPA, preferably from 0.02 to 0.09 MPA, more preferably from 0.02 to 0.09 MPA.

28. A method as claimed in any one of claims 25 to  
35 27, wherein the sintered ceramic-glass foam has a bulk porosity in the range of from 30 to 90%.

29. A method as claimed in any one of claims 25 to 28, wherein the sintered ceramic-glass foam has a strut density of at least 70% of the theoretical density of the ceramic.

5

30. A method as claimed in any one of claims 25 to 29, wherein the sintered ceramic-glass foam has a modal pore size in the range of from 100 to 500  $\mu\text{m}$ .

10

31. A glass-reinforced ceramic foam material whenever produced by a method as claimed in any one of claims 1 to 30.

15

32. A synthetic bone material which comprises a glass-reinforced ceramic foam material as claimed in claim 31.

20

33. A composition which comprises a glass-reinforced ceramic foam material as claimed in claim 31 or a synthetic bone material as claimed in claim 32 together with a pharmaceutically acceptable diluent or carrier.

25

34. A bone implant, filler, cement, tissue engineering scaffold, synthetic bone graft or drug-delivery device which comprises a glass-reinforced ceramic foam material as claimed in claim 31, a synthetic bone material as claimed in claim 32 or a composition as claimed in claim 33.

30

35. A glass-reinforced ceramic foam material as claimed in claim 31, a synthetic bone material as claimed in claim 32 or a composition as claimed in claim 33 for use in a method of treatment of the human or animal body by surgery or therapy.

35

36. A glass-reinforced ceramic foam material for use

in biomedical applications and comprising hydroxyapatite and a biocompatible glass and optionally a source of fluoride ions.

5

10

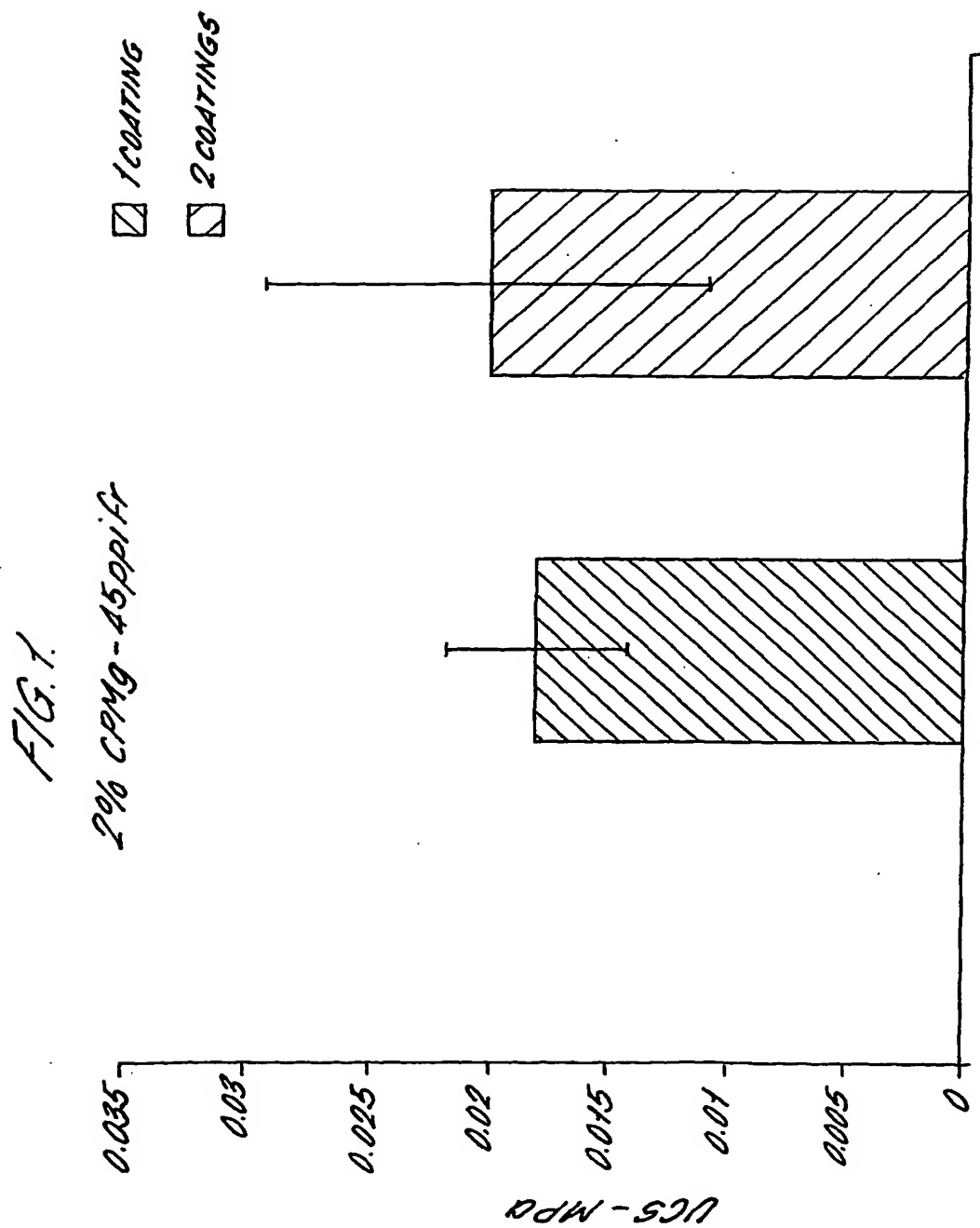
15

20

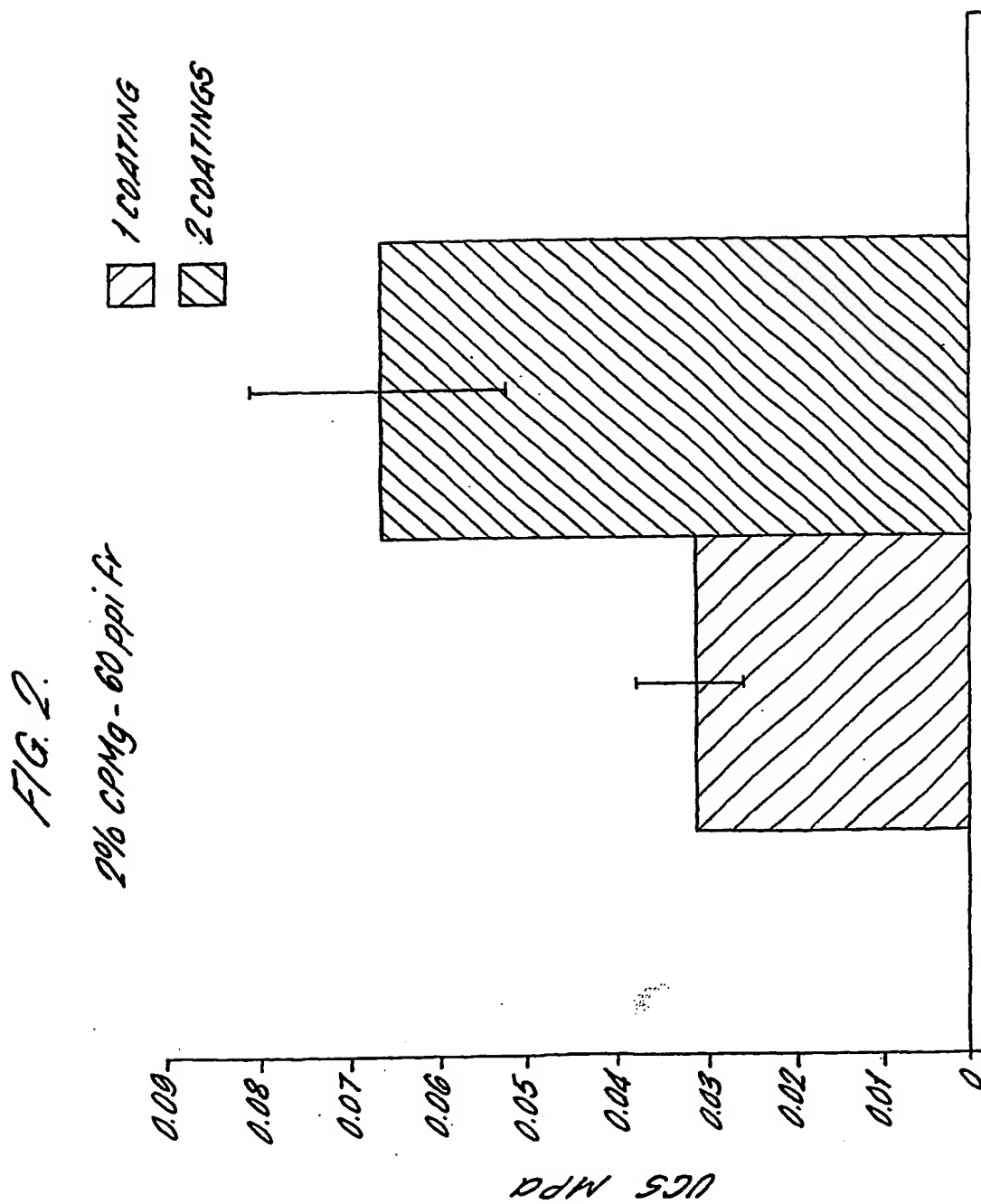
25

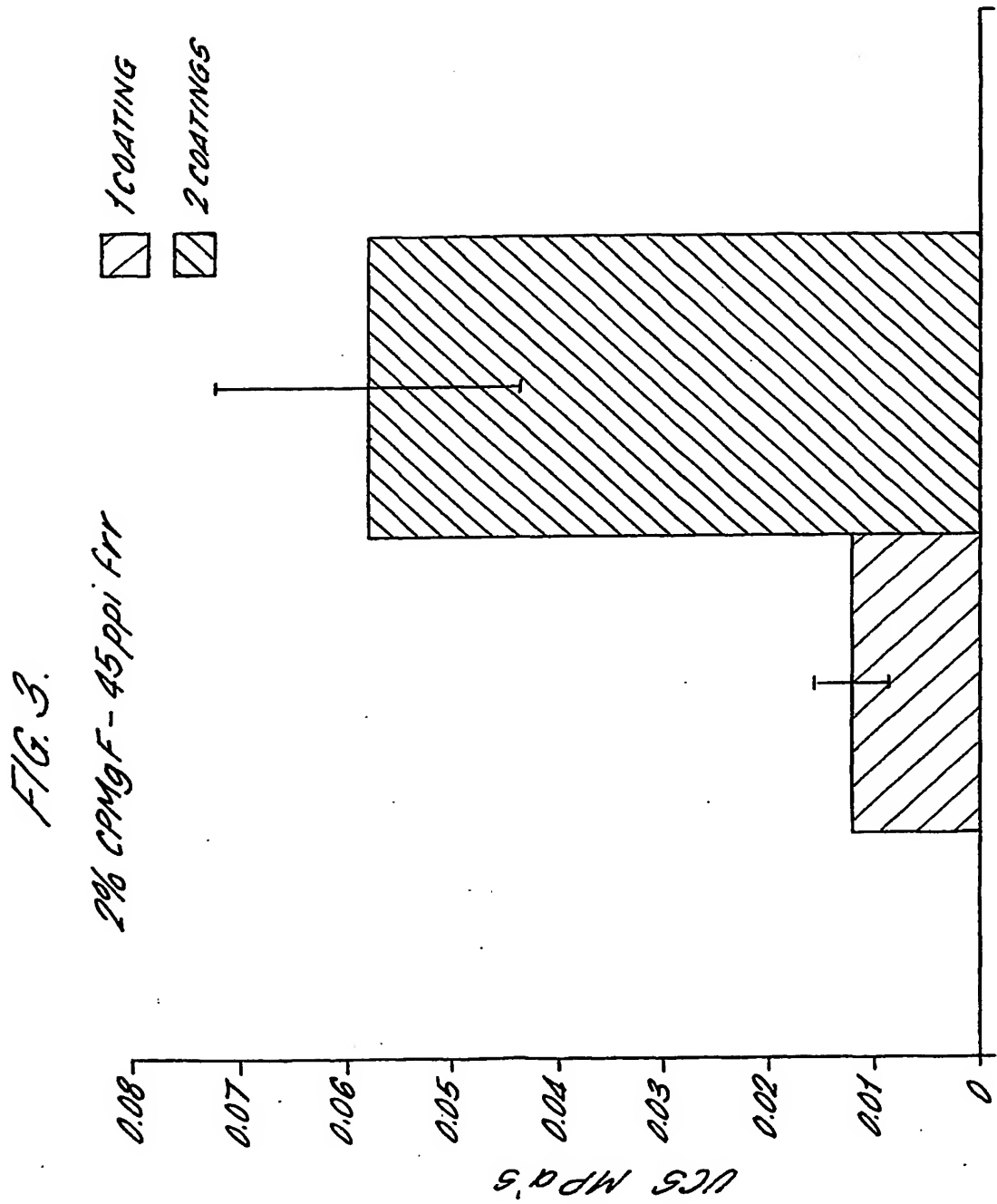
30

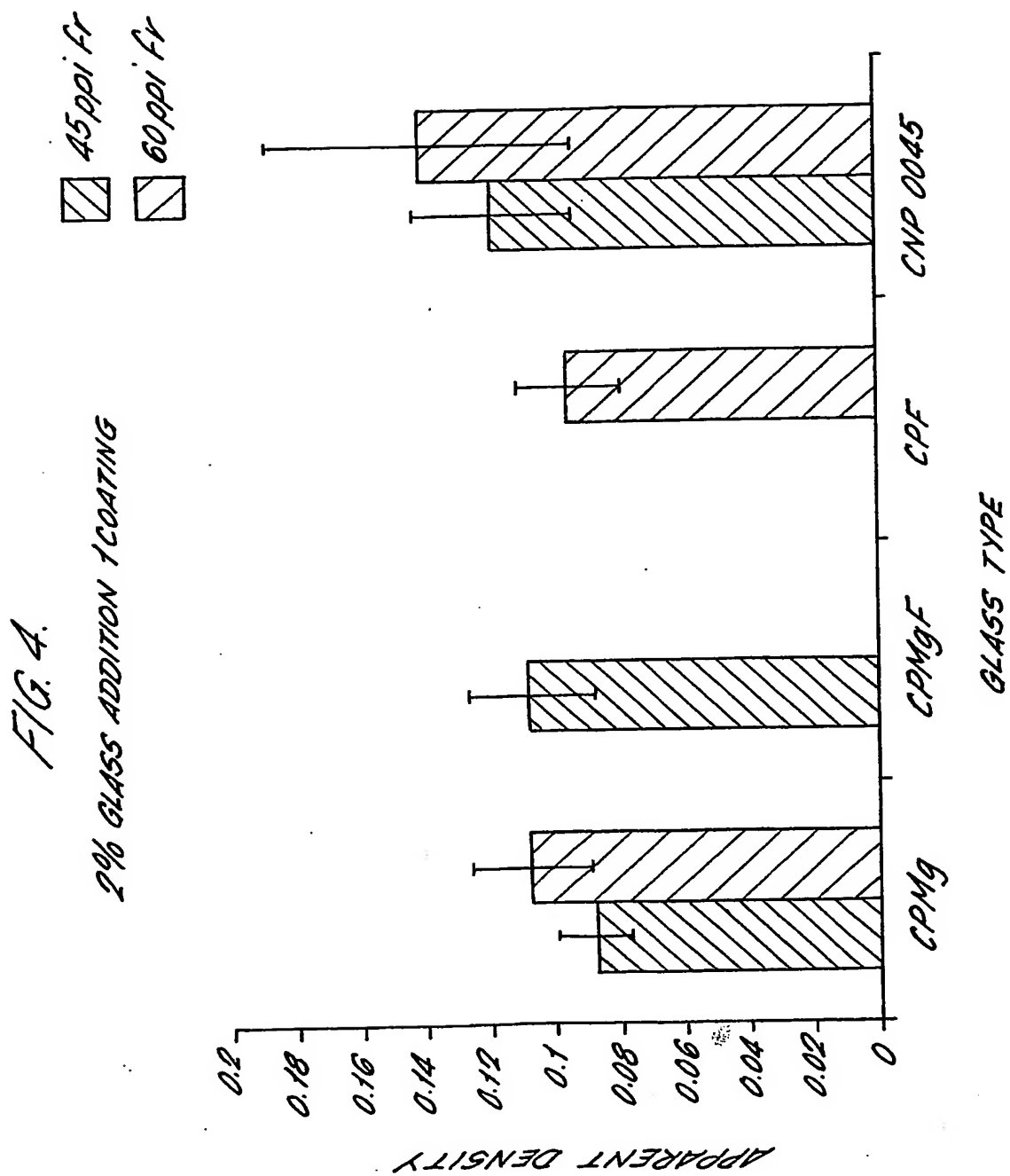
35

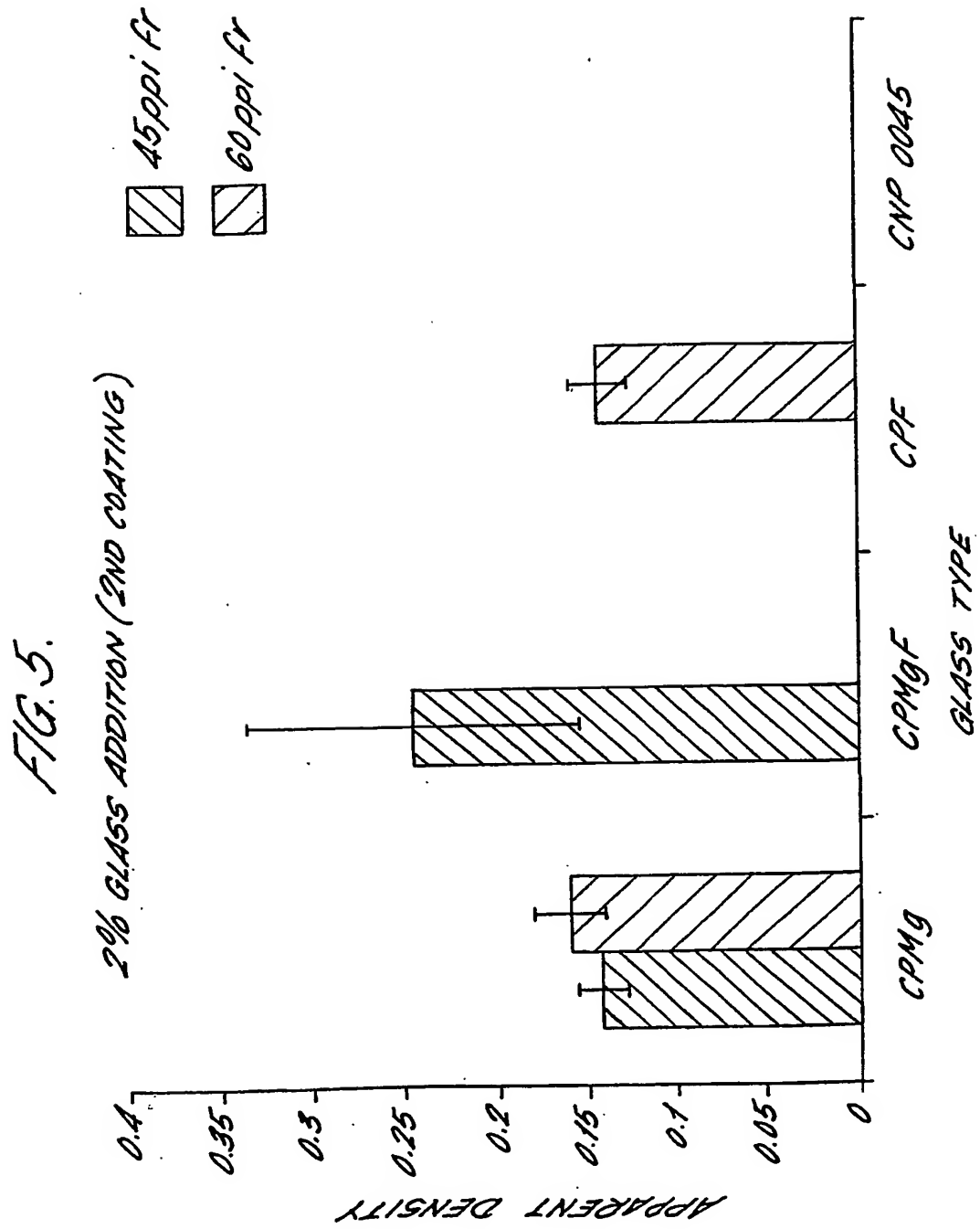




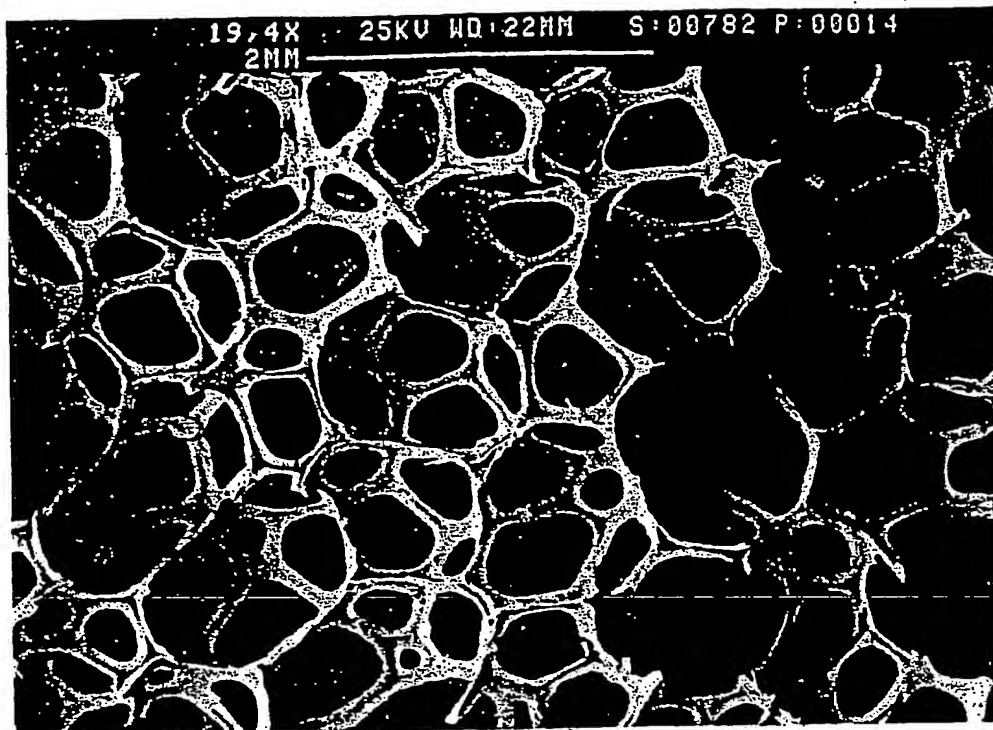








*FIG. 6.*



*FIG. 7.*

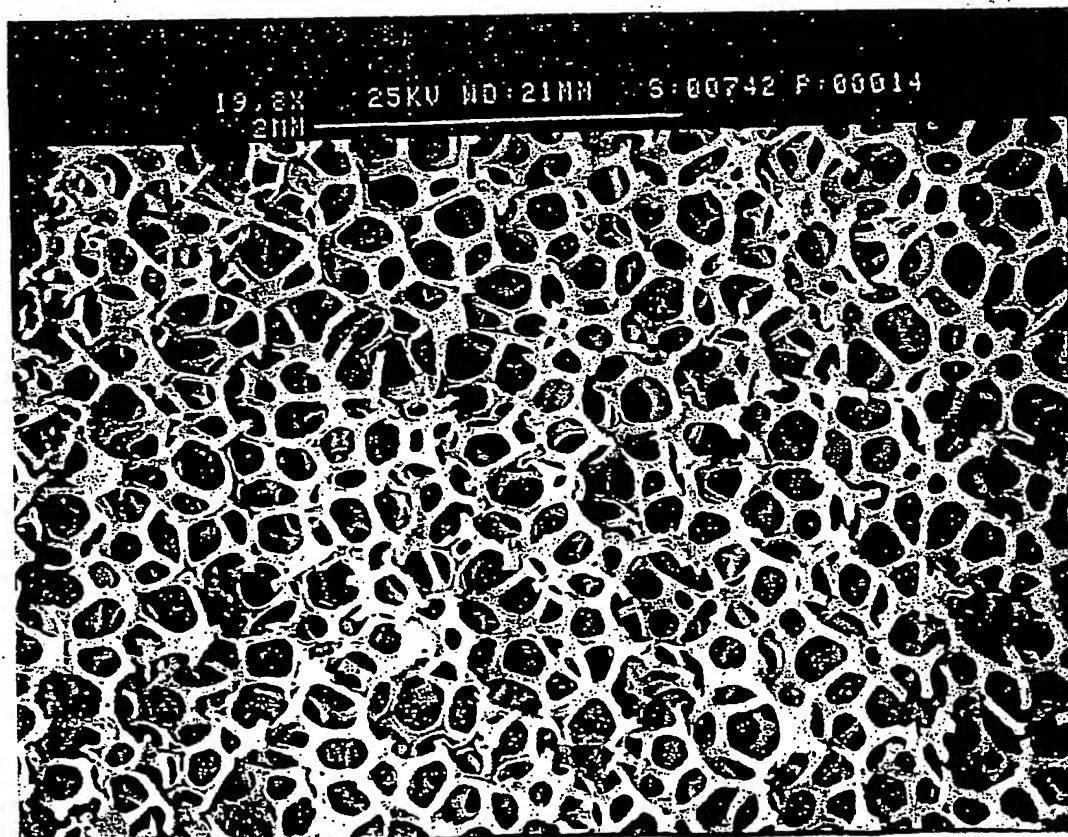


FIG. 8(a).

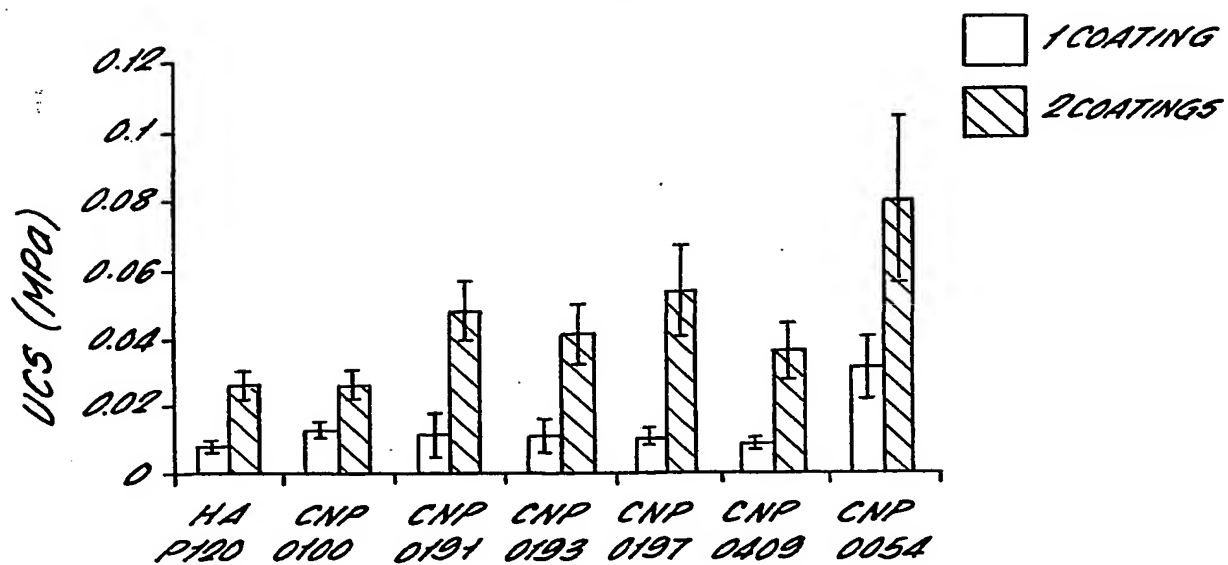
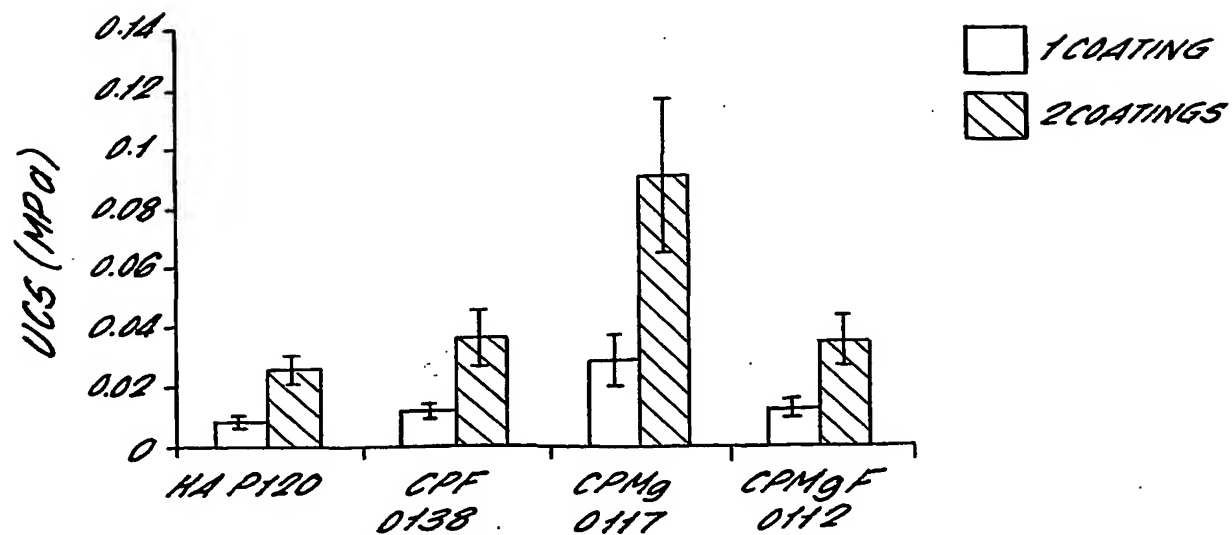


FIG. 8(b).



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 01/02507

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C04B38/06 C04B35/447 A61K6/033 A61L27/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C04B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 00 68164 A (KNOWLES JONATHAN CAMPBELL ;UNIV LONDON (GB); SILVA SANTOS JOSE DOM) 16 November 2000 (2000-11-16) claims	1, 13, 15-19, 31-36
Y	GB 2 078 696 A (MITSUBISHI MINING & CEMENT CO) 13 January 1982 (1982-01-13)  page 1, line 114 -page 2, line 30 page 2, line 103 - line 112; example 1	1, 13, 15-19, 31-36
A	WO 00 20353 A (HING KARIN ANGELA ;ABONETICS LTD (GB); BONFIELD WILLIAM (GB)) 13 April 2000 (2000-04-13) page 3, line 15 -page 4, line 20 page 5, line 4 - line 26 page 7, line 31 - line 34  -/-	1-3, 7, 8, 11, 12, 20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

11 September 2001

Date of mailing of the international search report

18/09/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Theodoridou, E

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 01/02507

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 118, no. 16, 19 April 1993 (1993-04-19) Columbus, Ohio, US; abstract no. 153026t, A.SLOSARCZYK ET AL.: "Manufacture of highly porous ceramics" XP000391666 abstract & PL 154 958 A (AKADEMIA GORNICZO-HUTNICZA IM. STANISLAWA STASZICA) 30 April 1992 (1992-04-30) -----	1,2,6,7, 21,25, 26,32,34
A	EP 0 577 342 A (QUEEN MARY & WESTFIELD COLLEGE) 5 January 1994 (1994-01-05) claims -----	1,13,19, 31,32,34



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/02507

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0068164	A	16-11-2000	GB 2349888 A AU 4768600 A WO 0068164 A1	15-11-2000 21-11-2000 16-11-2000
GB 2078696	A	13-01-1982	JP 1056777 B JP 1635901 C JP 56166843 A DE 3121182 A1 NL 8102354 A ,C	01-12-1989 31-01-1992 22-12-1981 04-02-1982 16-12-1981
WO 0020353	A	13-04-2000	AU 6111999 A EP 1117626 A1 WO 0020353 A1	26-04-2000 25-07-2001 13-04-2000
PL 154958	A		NONE	
EP 0577342	A	05-01-1994	EP 0577342 A1	05-01-1994